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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	RIGL-036CIP	5176

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-36* is/are pending in the application.

4a) Of the above claim(s) *26-29 and 31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26, 30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 17-36 are under examination.

Claims 26, 27-29, 31, 32 and claims 33-36 are withdrawn from consideration as being directed to non-elected inventions and species.

Claims 17-26, 30 and 32 (with respect to the elected species) are under examination.

Withdrawn Objection/Rejection

In view of applicants' arguments and telephonic interview together with SPE Schultz on 7/11/2007, the objection to the specification regarding the new matter issue is withdrawn. Also, the 35 USC 101 double patenting rejection over USP 6,897,031 is withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 17-24 and 30, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Uhr et al (USP 5612185) in view of Conneally et al(Blood) for reasons of record as reiterated below.

Uhr discloses at col. 3, line 30 up to col. 17, line 45:

Suitable techniques of multiparameter cell sorting will be known to those of skill in the art in light of the present disclosure. Generally speaking one contacts the population of tumor cells to be analyzed with a panel of antibodies directed against distinct cell surface molecules, under conditions effective to allow antibody binding. The antibodies employed would preferably be monoclonal antibodies, and would be labelled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths, it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal. Thus cells can be separated on the basis of ***6 parameters***. The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using fluorescence-activated flow cytometry.

FIG. 1. Flow cytometric identification of CCALC. Splenocytes from Id-immune control mice, Id-immune mice with CCALC, and non-immunized mice bearing clinically progressing BCL.sub.1 tumor were analyzed for their light scatter profile (left column), and their expression of Thy1 vs. .lambda. (middle column), and .kappa. vs. .lambda. (right column). 10,000 events, gated to exclude non-viable cells, are shown for each plot. In the left and middle columns, the .lambda..sup.+ /Thy1.sup.- population is colored red with the remaining cells gray. In the right column, the .lambda..sup.+ population is colored light blue or violet, delineating the .kappa..sup.+ or .kappa..sup.- subset, respectively. Flow cytometry was performed on a FACScan equipped with an argon ion laser tuned at 488 nm. Forward light scattering, orthogonal light scattering, FITC and PE signals were determined for 30,000 cells. Data was displayed with "paint-agate" software.

FIG. 2. A: Cell cycle analysis of CCALC vs. BCL.sub.1 tumor cells. Splenocytes from Id-immune mice with CCALC, and non-immunized mice bearing clinically progressing BCL.sub.1 tumor were simultaneously analyzed for their light scatter profile, DNA content (Hoechst 33342 staining), and expression of .lambda., Thy1, and Ia. 4300 events were collected gated on 1) the .lambda..sup.+ /Thy1.sup.- /Ia.sup.+ population, and 2) the width vs. area of the

Hoechst 33342 signal (pulse analysis), so as to eliminate doublets and larger cell aggregates. The scatter and DNA profile of the gated cells are shown in the left and right columns, respectively. Cells in the G.sub.0 /G.sub.1 -phase of the cell cycle (1n DNA content) are colored violet, those in S-phase (between the 1 and 2n peaks) are colored light blue, and those in G2/M-phase (2n DNA) are colored black. B,C: Morphology of BCL.sub.1 tumor cells (B) vs. CCALC (C). Splenocytes from Id-immune mice with CCALC, and non-immunized mice bearing growing BCL.sub.1 tumor were stained for their expression of .lambda., Thy1 and Ia, and the .lambda..sup.+ /Thy1.sup.- /Ia.sup.+ populations were sorted, cytocentrifuged onto slides, fixed with methanol and stained with Wright/Geimsa. Growing BCL.sub.1 cells (left panel; 750.times. magnification) have a large, immunoblast morphology with active-appearing nuclei (open chromatin and multiple, prominent nucleoli) and abundant gray cytoplasm. The great majority of CCALC (right panel; 750.times. magnification) are small to medium-sized and have eccentric, inactive nuclei (clumped chromatin with inconspicuous nucleoli) that gives the cells a plasmacytoid appearance. Occasional cells have a classical plasma cell morphology (open arrow). A minority of cells (closed arrow) are slightly larger with more active appearing nuclei, but are still clearly distinguishable from growing BCL.sub.1 cells. The distribution of Hoechst staining intensity was displayed with "paint-a-gate" software. For multiparameter cell sorting, a dual-laser FACStar Plus was used and the fluorochromes FITC, PE, allophycocyanin and Texas red.

Uhr discloses at col. 19, lines 16-45:

In the present study, the BCL.sub.1 tumor model was employed as a means to analyze in detail the cellular and molecular mechanisms underlying changes in malignant phenotypes. In particular, this model was employed to isolate dormant lymphoma cells for further analysis. High resolution, multiparameter flow cytometry was employed to identify and subsequently isolate (by fluorescent-activated cell sorting, FACS) dormant cells in the spleen. The technique is based on the assumption that, given appropriate markers, dormant cells will have a unique "signature" of physical and antigenic characteristics

> (qualitative and quantitative) that allow separation from normal splenocyte populations.
>
> A cytometry software program--PAINT-A-GATE--was utilized that allows the simultaneous analysis of cell surface density of 4 MAb-defined antigens and two scatter parameters (forward and orthogonal, which give information on cell size and complexity, respectively). This simultaneous analysis enables a search for unique clusters of cells in six-dimensional space that is consistent with a dormant tumor cell population, i.e., a population that expresses appropriate antigens and is present only in animals with dormant tumor. The inventors reasoned that using this technique, with a defined combination of MAbs, would lead to the identification of a unique cluster of cells which, when sorted, would be the only cells in the spleen capable of producing a BCL.sub.1 tumor in naive recipients.

Uhr does not disclose a retroviral vectors to which the population(library, as claimed) antibodies(bioactive agents, as claimed) are transfected. However, Conneally teaches in the entire reference, e.g., page 461, Discussion heading, that recombinant retroviuses offer many advantages for the genetic modification of human cells. One of the major advantages of the vector is the ability to assess gene transfer to specific subpopulations of cells immediately after infection. The detectable level is sorted by FACS. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use a retroviral vectors in the method of Uhr for the advantages taught by Conneally in using retroviral vectors. Said advantages would provide the motivation

to one having ordinary skill in the art at the time the invention was made in the use retroviral vectors.

Response to Arguments

Applicants submit that neither the Uhr nor Conneally reference teaches a library of retroviral vectors encoding different candidate bioactive agents, as required by the claims. As such, the combination of Uhr and Conneally fails to teach an element of the rejected claims.

In response, attention is drawn to the disclosure of Uhr at col. 22, lines 14-20:

> The preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is also contemplated. In this regard, replication defective ***retrovirus***, such as LNSX, LN or N2A, may be used, as may other ***vectors*** such as adenovirus or vaccinia viruses.

Uhr discloses a panel of c-fos and c-myc genes (the library of retroviral vectors encoding different bioactive agent, as broadly claimed). See further Fig. 3 and Example 2. The panel of c-fos and c-myc disclosed by Uhr would read on the claimed library. A library as defined in the instant specification, page 10, and lines 7-10 contains at least two (in this instance cells as disclosed, not a bioactive agent, as claimed). Accordingly, even Uhr alone discloses the claimed method. (The reference to antibodies as the bioactive agent above is regretted. A closer

review of the Uhr reference in its entirety clearly reveals that the bioactive agents are the genes encoding antigens.)

Claims 17-25, 30 and 32, as amended, are rejected under 35 U.S.C. 103(a) as being obvious over Nolan(WO 97/27212) in view of Jia-ping (Chinese Journal of Physical Medicine) and Uhr et al (USP 5612185) for reasons of record as repeated below.

Nolan et al discloses at page 31, line 1 up to page 32, line 6:

> The methods of the present invention comprise introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The plurality of cells is then screened, as is more fully outlined below, for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent.
>
> By "altered phenotype" or "changed physiology" or other grammatical equivalents herein is meant that the phenotype of the cell is altered in some way, preferably in some detectable and/or measurable way. As will be appreciated in the art, a strength of the present invention is the wide variety of cell types and potential phenotypic changes which may be tested using the present methods. Accordingly, any phenotypic change which may be observed, detected, or measured may be the basis of the screening methods herein. Suitable phenotypic changes include, but are not limited to: gross physical changes such as changes in cell morphology, cell growth, cell viability, adhesion to substrates or other cells, and cellular density; changes in the expression of one or more RNAs, proteins, lipids, hormones, cytokines, or other molecules; changes in the equilibrium state (i.e. half-life) or one or more RNAs, proteins, lipids, hormones, cytokines, or other molecules; changes in the localization of one or more RNAs, proteins,

lipids, hormones, cytokines, or other molecules; changes in the bioactivity or specific activity of one or more RNAs, proteins, lipids, hormones, cytokines, receptors, or other molecules; changes in the secretion of ions, cytokines, hormones, growth factors, or other molecules; alterations in cellular membrane potentials, polarization, integrity or transport; changes in infectivity, susceptability, latency, adhesion, and uptake of viruses and bacterial pathogens; etc. By "capable of altering the phenotype" herein is meant that the bioactive agent can change the phenotype of the cell in some detectable and/or measurable way.

The altered phenotype may be detected in a wide variety of ways, as is described more fully below, and will generally depend and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example: microscopic analysis of cell morphology; standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds after killing the cells; etc. In some cases, as is more fully described herein, the altered phenotype is detected in the cell in which the randomized nucleic acid was introduced; in other embodiments, the altered phenotype is detected in a second cell which is responding to some molecular signal from the first cell.

In a preferred embodiment, once a cell with an altered phenotype is detected, the cell is isolated from the plurality which do not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, ***FACS***, lysis selection using complement, cell cloning, scanning by Fluorimager, expression of a "survival" protein, induced expression of a cell surface protein or other molecule that can be rendered fluorescent or taggable for physical isolation; expression of an enzyme that changes a non-fluorescent molecule to a fluorescent one; overgrowth against a background of no or slow growth; death

> of cells and isolation of DNA or other cell vitality indicator dyes, etc.

See further the Examples, which describes the method in detail.

Nolan is discussed above. Nolan does not disclose a method in which the cellular phenotype is exocytosis and a 5-parameter cell sorting by FACS (although suggests said FACS analysis). However, Jia-ping discloses a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increased of purity of the divided cell and further information of the different cell subpopulations that can be obtained (page I). Uhr discloses at col. 3, line 30:

> Suitable techniques of multiparameter cell sorting will be known to those of skill in the art in light of the present disclosure. Generally speaking one contacts the population of tumor cells to be analyzed with a panel of antibodies directed against distinct cell surface molecules, under conditions effective to allow antibody binding. The antibodies employed would preferably be monoclonal antibodies, and would be labelled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths, it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal. Thus cells can be separated on the basis of ***6 parameters***. The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using fluorescence-activated flow cytometry.
>
> Uhr discloses at col. 19, lines 16-45:

> The technique is based on the assumption that, given appropriate markers, dormant cells will have a unique "signature" of physical and antigenic characteristics (qualitative and quantitative) that allow separation from normal splenocyte populations.
>
> A cytometry software program--PAINT-A-GATE--was utilized that allows the simultaneous analysis of cell surface density of 4 MAb-defined antigens and two scatter parameters (forward and orthogonal, which give information on cell size and complexity, respectively). This simultaneous analysis enables a search for unique clusters of cells in six-dimensional space that is consistent with a dormant tumor cell population, i.e., a population that expresses appropriate antigens and is present only in animals with dormant tumor. The inventors reasoned that using this technique, with a defined combination of MAbs, would lead to the identification of a unique cluster of cells which, when sorted, would be the only cells in the spleen capable of producing a BCL.sub.1 tumor in naive recipients.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the parameter exocytosis phenotype change and at least 5 parameters of the cell in the method of Nolan in the manner as taught by Jia-ping and Uhr. One having ordinary skill in the art would haye been motivated to sort the cells by at least 5 parameters including exocytosis for the advantages taught by Jia-ping and Uhr above. (The sorting of cells by FACS is known in the art as recognized by applicants' discussion in the BACKGROUND OF THE INVENTION at page 1, lines 25-28 of the instant disclosure).

[Applicants' arguments over Nolan et al (USP 6455247) are moot in view of the new ground of rejection, above.]

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping (Chinese Journal of Physical Medicine) and Uhr et al as applied to claims 17-25, 30 and 32 above, and further in view of Hide et al(Jrnl. of Cell Biology) and applicants' disclosure of known art.

Nolan is discussed, above. Nolan discloses FACS means of measuring the altered cellular phenotype except the claimed recitation that the exocytosis is measured by annexin granule binding. However, Hide discloses e.g., at page 488, col. 2 that cells (mast) contain large numbers of secretory granules which makes them highly refractile which is manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of (mast) cells. Applicants at page 38, lines 10-20 admit that annexin is commercially available. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis by annexin granule binding as taught by Hide. Hide

teaches that exocytosis measured by granule binding is one of the means of classifying cell populations (and appears to be a sensitive measure of the cell behavior as shown by its high refractile property). Applicants' admit in the instant disclosure that annexin is commercially available. Thus, it would be within the ordinary skill in the art at the time the invention was made to use compounds that are commercially or conventionally used in the art with a reasonable expectation of success in identifying cells with a change in said parameter.

Response to Arguments

Applicants refer to the response of July 24, 2006 (which is responsive to the Office Action dated February 24, 2006), in which Nolan was addressed. Summarizing their prior response, Nolan 's publication date (July 31, 1997) predates the earliest priority date of this application (April 17, 1997). As such, Nolan qualifies as prior art only under 35 U.S.C. § 102(a)

A Declaration under 35 U.S.C. § 1.131 (the "Fisher declaration") was submitted with the Applicants' response of July 24, 2006, in order to obviate a rejection over a near identical combination of references (i.e., Nolan in view of ~Jai-ping or Ryan). The declaration established invention of the subject matter of the rejected claims prior to the Nolan publication date, In view of the foregoing discussion, the

Applicants submit that Nolan is disqualified as a prior art reference and cannot preclude the patentability of the instant claims.

In response, the Nolan reference (WO 97/27212, not the US 6455247 patent was used in the above rejection) was published more than one year of applicants' earliest filing date. Thus, the 35 USC 1.131 declaration does not overcome the 103 rejection based on 102(b) rejection over the Nolan reference as Nolan (WO 97/27212) is a bar against the instant application.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 26, 27-29, 31, 32 and claims 33-36 drawn to a nonelected invention. A complete reply

to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw

August 3, 2007